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Studies on the Synthesis of Penazetidine A, an Alkaloid Inhibitor of Protein Kinase C

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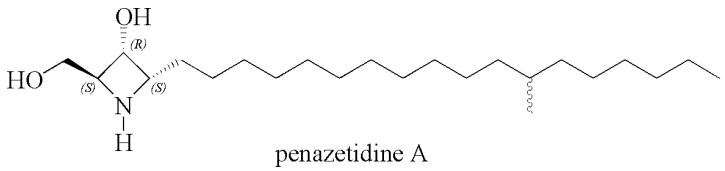
Abstract: A convergent asymmetric synthesis of (2S, 3R, 4S, 12'R)-3-hydroxy-2-hydroxymethyl-4-(12' -methyloctadecyl)-N-(*p*-tolylsulfonyl)-azetidine, a key precursor of penazetidine A, has been achieved by starting from divinylcarbinol.

Keywords: Penazetidine A, alkaloid, azetidine, Wittig reaction.

Penazetidine A, an alkaloid inhibitor of protein kinase C (PKC), was first isolated by Phillip Crews and coworkers in 1994[1]. With an IC_{50}=1μmol/L, it is one of a few compounds to show specific rat brain PKCβ1 inhibition [1].

Figure 1



penazetidine A

However, relatively few reports can be found regarding the synthesis of penazetidine A. In 1996, Mori and his coworkers reported the first synthesis of it, and confirmed the structure of the substituted azetidine as (2S, 3R, 4S)[2]. Knapp and his coworkers synthesized the 16-nor analogue of penazetidine A in 1997[3]. They employed chiral pool reagents. In this letter, we wish to report the convergent synthesis of (2S, 3R, 4S,12'R)-3-hydroxy-2-hydroxymethyl-4-(12'-methyloctadecyl)-N-(*p*-tolylsulfonyl)-azeti dine, a precursor of penazetidine A, from an achiral compound divinylcarbinol.

The strategy of synthesis of azetidine building block **5** is similar to the synthesis of penaresidin A reported by us[4](**Scheme 1**). The crude **5**, one of the key intermediates for penazetidine A was used directly in the next step without further purification. The construction of the side chain **13** and remaining steps leading to **16** were summarized in **Scheme 2**. (－)-Sultam **6**, obtained from (+)-S-camphorsulfonic acid[5,6], was used as

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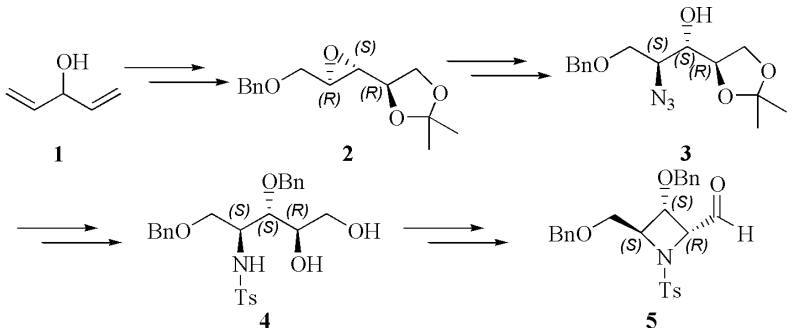
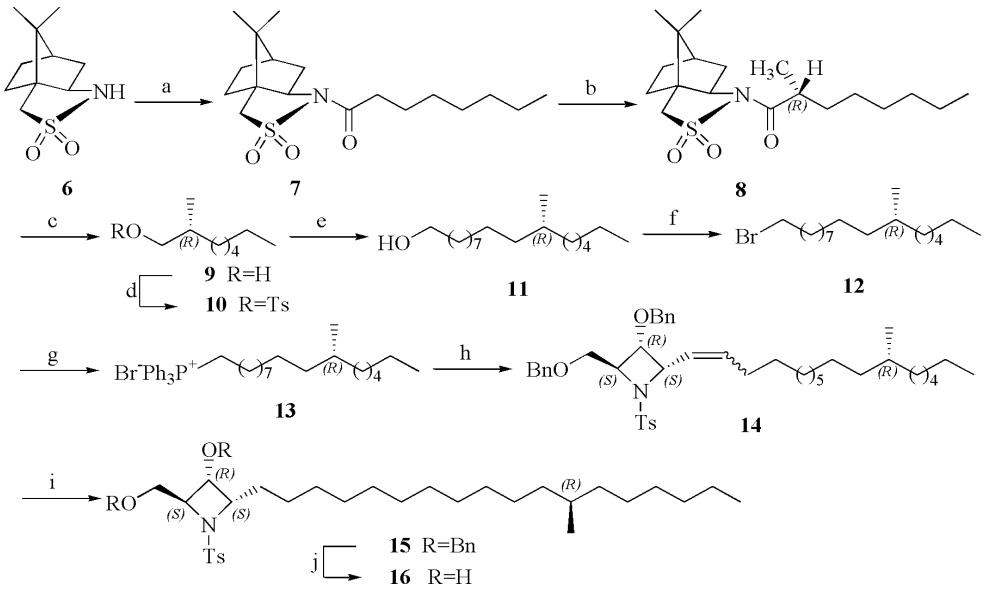
Scheme 1



Scheme 2



Reagents and conditions: a) NaH, octanoyl chloride, toluene, 88%; b) *n*-BuLi, MeI, HMPA, THF, −78°C, 96%; c) $LiAlH_4$, THF, 0°C, 93% (96% e.e.); d) TsCl, Pyr, CH_2Cl_2, 0°C, 96%; e) i. $BrMg(CH_2)_8CH_2OTHP$, Li_2CuCl_4, THF; ii. PTS, CH_3OH, 73%(2 steps); f) NBS, PPh_3, DMF, CH_3OH, 95%. g) PPh_3, CH_3CN, reflux, 86%; h) **5**, *n*-BuLi, THF, −78°C, 60%; i) NH_2OH, EtOAc, DMF, 90-100°C, 98%; j) 10% Pd/C, H_2, 95% EtOH, 86%.

chiral template. Chiral alcohol **9** was obtained[7] in 79% yield (96% e.e.) *via* 3 steps. The tosylate **10** was derived from **9** with 9-tetrahydropyranoxy-1-nonyl magnesium bromide[8] followed by the removal of the protective group THP to furnish alcohol **11**. Bromination of **11** and subsequent conversion to Wittig reagent **13**, providing another fragment for Wittig reaction. With the two segments **13** and **5** in hand, the Wittig reaction was carried out with *n*-BuLi as the base to obtain **14**. The double bond in **14** was reduced with diimide to give compound **15**. Finally, the benzyl protective groups were removed smoothly by hydrogenolysis(10% Pd/C) to afford the target compound **16**[9] as a colorless oil. The overall yield of **16** was 6.0% based on divinylcarbinol.

References and Notes

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8. Synthesis of 9-tetrahydropyranoxy-1-nonyl magnesium bromide: commercially available 9-bromononanol was protected as DHP derivative, and was subsequently converted to Grignard reagents.
9. Properties of compound **16**: $[\alpha]_D^{20}$ +5.4 (c 0.40, $CHCl_3$); IR (film) *v* : 3399 (br, OH), 2924, 2853, 1460, 1332, 1153, 1093, 1020, 814; ^{1}H NMR ($CDCl_3$, 500 MHz) δ_{ppm} : 0.84 (d, 3H, *J*=6.5 Hz, H-23), 0.88 (t, 3H, *J*=6.8 Hz, H-22), 1.09 (m, 2H, H-15,17), 1.09-1.40 (m, 31H, H-5, 6,7,8,9,10,11,12,13,14,15,16,17), 2.44 (s, 3H, Ar-CH_3), 3.80 (dd, 1H, *J*= 12.8, 4.4 Hz, H-1), 3.95-4.02 (m, 2H), 4.33-4.38 (m, 1H, H-4), 4.50 (dd, 1H, *J*=6.6, 4.7 Hz, H-3), 7.29 (d, 2H, *J*=8.1 Hz, Ar-H), 7.73 (d, 2H, *J*=8.2 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_{ppm}: 14.1 (C-22), 19.7 (C-23), 21.6 (Ar-CH_3), 22.7 (C-21), 25.9 (C-6), 27.0 (C-5), 29.6 (C-14,18), 29.8 (C-7,8,9,10,11, 12,19), 30.1 (C-13), 32.0 (C-20), 32.8 (C-16), 37.1 (C-15,17), 62.2 (C-1), 65.0 (C-4), 68.9 (C-3), 74.2 (C-2), 127.4 (Ar-C), 129.8 (Ar-C), 137.1 (Ar-C), 143.8 (Ar-C); EIMS (70 eV) *m/z* (%) : 523 (0.26), 522 (0.21), 492 (1.51), 464 (1.45), 450 (59), 436 (4.58), 368 (3.28), 214 (40), 155 (72), 121 (16), 91 (100); HREIMS calcd. for $C_{30}H_{53}NO_4S$ 523.3695, found 523.3725.

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